## DRUGDEX® Evaluations

# LOTEPREDNOL

## 0.0 Overview

1) Class
   a) This drug is a member of the following class(es):
      Adrenal Glucocorticoid
      Ophthalmologic Agent
2) Dosing Information
   a) Loteprednol Etabonate
      1) Adult
         a) Allergic conjunctivitis, Seasonal
            1) 0.2% suspension, 1 drop in affected eye(s) 4 times a day
         b) Inflammatory disorder of the eye, Post-operative
            1) 0.5% suspension, 1-2 drops in affected eye 4 times/day, starting 24 hr after surgery and continuing for 2 wk
         c) Inflammatory disorder of the eye, Steroid-responsive
            1) 0.5% suspension, 1-2 drops in affected eye(s) 4 times a day
      2) Pediatric
         a) Safety and effectiveness in children not established
3) Contraindications
   a) Loteprednol Etabonate
      1) Hypersensitivity to loteprednol products or corticosteroids
      2) Ocular viral, mycobacterial or fungal infections
4) Serious Adverse Effects
   a) Loteprednol Etabonate
      1) Cataract
      2) Eye infection, Secondary
      3) Raised intraocular pressure
5) Clinical Applications
   a) Loteprednol Etabonate
      1) FDA Approved Indications
         a) Allergic conjunctivitis, Seasonal
         b) Inflammatory disorder of the eye, Post-operative

c) Inflammatory disorder of the eye, Steroid-responsive

# 1.0 Dosing Information

Drug Properties
Adult Dosage
Pediatric Dosage

## 1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
B) Synonyms
Loteprednol
Loteprednol Etabonate
C) Physicochemical Properties
1) Molecular Weight
a) 466.96 (Prod Info Alrex, 98) (Prod Info Lotemax, 98)
2) pH
a) Ophthalmic: Ophthalmic suspension: 5.3 to 5.6 (Prod Info Alrex, 98) (Prod Info Lotemax, 98).
3) Ophthalmic: Tonicity: 250 to 310 milliosmoles per kg of body weight (mOsmol/kg) (Prod Info Alrex, 98) (Prod Info Lotemax, 98).

## 1.3 Adult Dosage

### 1.3.1 Normal Dosage

#### 1.3.1.A Loteprednol Etabonate

##### 1.3.1.A.1 Ophthalmic route

a) The recommended dose of loteprednol etabonate 0.5% ophthalmic suspension in the treatment of steroid-responsive CONJUNCTIVITIS is one to two drops into the conjunctival sac of the affected eye four times daily. For the first week, the dose may be increased to 1 drop per hour. Shake applicator bottle vigorously before each use (Prod Info Lotemax(TM), 1998b).
b) The recommended dose of loteprednol etabonate 0.5% ophthalmic suspension in the treatment of POSTOPERATIVE CONJUNCTIVITIS is one to two drops into the conjunctival sac of the affected eye four times daily beginning 24 hours after surgery and continuing for two weeks. Shake applicator bottle vigorously before each use (Prod Info Lotemax(TM), 1998b).
c) The recommended dose of loteprednol etabonate 0.2% ophthalmic suspension to treat SEASONAL ALLERGIC CONJUNCTIVITIS is one drop into the affected eye four times daily. Shake applicator bottle vigorously before each use (Prod

Info Alrex(TM), 1998).
d) One drop of a 0.5% ophthalmic suspension of loteprednol etabonate four times daily has been administered to patients with contact lens-associated GIANT PAPILLARY CONJUNCTIVITIS. Some patients in this study continued contact lens wear during treatment; lenses were removed prior to each instillation, and reinserted 10 to 15 minutes later (Bartlett et al, 1993b).
e) LOTEPREDNOL ETABONATE/TOBRAMYCIN OPHTHALMIC SUSPENSION: 1 or 2 drops into the conjunctival sac of the affected eye(s) every 4 to 6 hours. During the initial 24 to 48 hours, the dosing may be increased, to every 1 to 2 hours for the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. As warranted by improvement in clinical signs, the frequency of administration should be decreased gradually. Therapy should not be discontinued prematurely. Shake vigorously before using (Prod Info ZYLET(TM) ophthalmic suspension, 2004).
f) Not more than 20 milliliters should be prescribed initially and the prescription should not be refilled without further evaluation (Prod Info ZYLET(TM) ophthalmic suspension, 2004).

## 1.4 Pediatric Dosage

### 1.4.1 Normal Dosage

#### 1.4.1.A Loteprednol Etabonate

##### 1.4.1.A.1 Ophthalmic route

a) LOTEPREDNOL ETABONATE/TOBRAMYCIN OPHTHALMIC SUSPENSION: Safety and efficacy have not been established (Prod Info ZYLET(TM) ophthalmic suspension, 2004).

# 2.0 Pharmacokinetics

Onset and Duration
Drug Concentration Levels
ADME

## 2.1 Onset and Duration

A) Onset
1) Peak Response
a) Contact lens-associated giant papillary conjunctivitis, ophthalmic: 1 week (Bartlett et al, 1993).

## 2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) After ocular administration, plasma levels of loteprednol etabonate and its metabolites are below measurable limits (Prod Info Lotemax(TM), 1998a; Howes & Novack, 1998).

## 2.3 ADME

Absorption
Distribution
Metabolism
Excretion
Elimination Half-life

### 2.3.1 Absorption

A) Bioavailability
1) Oral: minimal (Hochhaus et al, 1992).

### 2.3.2 Distribution

A) Distribution Sites
1) Protein Binding
a) 95% (Hochhaus et al, 1992).
2) OTHER DISTRIBUTION SITES
a) BLOOD, significant (Hochhaus et al, 1992).

### 2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) EYE, extensive (Druzgala et al, 1991).
a) One study in rabbits reported that extensive esterase metabolism of loteprednol etabonate to PJ-90 and PJ-91 occurs in the eye (mainly the cornea) following ocular instillation (Druzgala et al, 1991). It is unclear from this study if any unchanged drug was absorbed systemically. The metabolic profile of loteprednol etabonate in humans has not been investigated.
b) Results of animal studies are conflicting; both rapid and very slow (or lack of) esterase metabolism of loteprednol etabonate in blood and plasma have been reported (rats and dogs, respectively) (Hochhaus et al, 1992; Bodor et al, 1992). There is evidence that the minimal propensity of loteprednol etabonate to induce systemic adverse effects after absorption may be related more to its high degree of binding to plasma proteins and erythrocytes, and complete extraction and metabolism by the liver, than to rapid plasma hydrolysis (Hochhaus et al, 1992; Sloan & Perrin, 1994).
B) Metabolites
1) delta-1 cortienic acid etabonate (PJ-91), inactive (Prod Info Lotemax(TM), 1998a; Bodor et al, 1992; Hochhaus et al, 1992; Druzgala et al, 1991).
2) 17-beta carboxylic acid derivative, inactive (Hochhaus et al, 1992).

a) The design of loteprednol etabonate suggests that rapid esterase hydrolysis of the metabolically-labile 17-beta-chloromethyl ester function would occur in plasma following systemic absorption, forming the more hydrophilic and inactive 17-beta-carboxylic acid derivative (PJ-91) and subsequently delta-1-cortienic acid (PJ-90) (Hochhaus et al, 1992; Druzgala et al, 1991; Bodor et al, 1992).
b) Based on plasma and urinary excretion data in animals, the metabolism of loteprednol etabonate (whatever the mechanism) after its absorption appears to be complete or near-complete; the primary metabolite in plasma and urine (oral or intravenous) and the eye (topical) is PJ-91 (Druzgala et al, 1991; Bodor et al, 1992; Hochhaus et al, 1992).

**2.3.4 Excretion**

A) Kidney
1) Renal Excretion (%)
a) 0% (Hochhaus et al, 1992)

**2.3.5 Elimination Half-life**

A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 2.8 hours (Hochhaus et al, 1992).

# 3.0 Cautions

Contraindications
Precautions
Adverse Reactions
Teratogenicity/Effects in Pregnancy/Breastfeeding

## 3.1 Contraindications

A) Loteprednol Etabonate
1) Hypersensitivity to loteprednol products or corticosteroids
2) Ocular viral, mycobacterial or fungal infections

## 3.2 Precautions

A) Loteprednol Etabonate
1) Acute purulent conditions of the eye, steroids may mask infection or enhance existing infection (Prod Info ZYLET(TM) ophthalmic suspension, 2004)
2) Cataracts
3) Cross-sensitivity to other aminoglycoside antibiotics may occur (combination loteprednol/tobramycin ophthalmic suspension) (Prod Info ZYLET(TM) ophthalmic suspension, 2004)

4) Diabetes mellitus
5) Glaucoma
6) History of herpes simplex eye infection (Prod Info ZYLET(TM) ophthalmic suspension, 2004)
7) If signs and symptoms fail to improve after 2 days, the patients should be re-evaluated (combination loteprednol/tobramycin ophthalmic suspension) (Prod Info ZYLET(TM) ophthalmic suspension, 2004)
8) Intraocular hypertension
9) Prolonged use of antibiotics, may result in overgrowth of nonsusceptible organisms, including fungi (combination loteprednol/tobramycin ophthalmic suspension) (Prod Info ZYLET(TM) ophthalmic suspension, 2004)
10) Prolonged use of steroids may result in secondary ocular infections (including fungal infections of the cornea); glaucoma with damage to optic nerve; defects in visual acuity and fields of vision; and in posterior subcapsular cataract formation (Prod Info ZYLET (TM) ophthalmic suspension, 2004)
11) Thinning of the sclera or cornea
12) Viral infections of the eye (including herpes simplex) (Prod Info ZYLET(TM) ophthalmic suspension, 2004))

## 3.3 Adverse Reactions

### 3.3.10 Ophthalmic Effects

#### 3.3.10.A Loteprednol Etabonate

Eye / vision finding
Intraocular pressure finding

##### 3.3.10.A.1 Eye / vision finding

a) The most commonly reported ocular effects (5% to 15% of patients) associated with loteprednol etabonate include BLURRED VISION, discharge, DRY EYES, and burning on instillation (Prod Info Lotemax(TM), 1998).

##### 3.3.10.A.2 Intraocular pressure finding

a) Summary

1) There is some evidence that increases in intraocular pressure with ophthalmic use of loteprednol etabonate are minimal, and less than with conventional topical corticosteroids (Novack et al, 1998; Bartlett et al, 1993aa; Bartlett et al, 1993a). Increased intraocular pressure may have secondary complications such as optic nerve damage, decreased visual acuity, subcapsular cataract formation, ocular infections (including herpes simplex), and thinning of the cornea or sclera resulting in perforation (Prod Info Lotemax(TM), 1998).

b) Loteprednol etabonate 0.2% is a safe topical corticosteroid for long- term treatment of seasonal and perennial allergic conjunctivitis. In a retrospective chart review, 159 patients (aged 8 to 92 years) using loteprednol etabonate 0.2% daily (1 to 4 times daily) for at least 1 year were assessed. The number of drops per eye per duration of therapy ranged from 120 to 3741.

Intraocular pressure (IOP) increased significantly compared to baseline in 20 of 39 patients treated for 30 months, with an average maximum IOP of 18.33 millimeters of mercury (mmHg) (Ilyas et al, 2004).

**c)** In a multi-study analysis of patients and subjects enrolled in domestic, double-blind, manufacturer-sponsored studies, loteprednol etabonate ophthalmic suspension was less likely than prednisolone acetate to cause clinically significant (10 mmHg or greater) increases in intraocular pressure (IOP) when used long-term. Among 2210 subjects and patients, 1648 received either loteprednol etabonate 0.2% or 0.5% (n=901), prednisolone acetate 1% (n=164), or placebo vehicle (n=583) for 28 days or longer. Known corticosteroid responders were excluded from all studies. The incidence of significantly increased IOP was 1.7% in the loteprednol group, 6.7% in the prednisolone group, and 0.5% in the placebo group. After excluding contact-lens wearers, the incidences were 0.6% in the loteprednol group, 6.7% in the prednisolone group, and 1% in the placebo group (Novack et al, 1998).

**d)** In a small double-blind comparison of loteprednol with prednisolone in known steroid responders (previous intraocular pressure elevations with topical steroid use), ophthalmic loteprednol 0.5% suspension instilled 4 times daily over 6 weeks produced a mean increase in intraocular pressure of 4.1 mmHg; this increase was near statistical significance compared with baseline. Administration of prednisolone 1% ophthalmic suspension produced mean elevations of 5.9, 7.7, and 9 mmHg above baseline on days 14, 28, and 42, respectively. These changes were barely significant relative to baseline values (Bartlett et al, 1993aa). This study failed to statistically compare pressure changes between loteprednol and prednisolone (most likely as they were not statistically significant). Furthermore, the loteprednol etabonate dose concentration was lower than that of prednisolone. A similar concentration between active treatments may have induced greater intraocular pressure increases. In the limited preclinical comparative data available, a 1% concentration of loteprednol etabonate only approached the anti-inflammatory activity of 1% prednisolone (Bartlett et al, 1993a; Bartlett et.al, 1993aa).

## 3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Lotemax(R), 2002) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) Loteprednol has been shown to be embryotoxic and teratogenic when administered orally to rabbits during organogenesis (Prod Info Lotemax(R), 2002). Therefore, loteprednol should only be used during pregnancy if the maternal benefit outweighs the possible risk to the fetus.

4) Literature Reports

a) Rats given loteprednol orally during organogenesis at doses greater than 5 mg/kg/day and 50 mg/kg/day delivered pups with teratogenic effects. Embryotoxicity was also observed at 100 mg/kg/day, with skeletal ossification and decreased body weight seen

with doses greater than 50 mg/kg/day. Rats given 0.5 mg/kg/day (6 times the maximum recommended human dose) did not show impaired reproductive capacity. Rats given loteprednol 50 mg/kg/day from the start of gestation through lactation experienced maternal toxicity and delivered pups with decreased growth and survival and slowed development (Prod Info Lotemax(R), 2002).

B) Breastfeeding
  1) Thomson Lactation Rating: Infant risk cannot be ruled out.
    a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.
  2) Clinical Management
    a) It is not known whether significant amounts of loteprednol would be systemically absorbed after ophthalmic administration. Maternal use of topical preparations generally carries less risk than systemically administered drug; risk to the infant should be considered relative to the inherent toxicity of the drug. Loteprednol should only be used during pregnancy if the maternal benefit outweighs the possible risk to the fetus.
  3) Literature Reports
    a) No reports describing the use of loteprednol during human lactation or measuring the amount, if any, of the drug excreted into milk have been located.

## 4.0 Clinical Applications

Monitoring Parameters
Patient Instructions
Place In Therapy
Mechanism of Action / Pharmacology
Therapeutic Uses
Comparative Efficacy / Evaluation With Other Therapies

### 4.1 Monitoring Parameters

A) Loteprednol Etabonate
  1) Therapeutic
    a) Physical Findings
      1) Clinical improvement of condition being treated; re-evaluate patient if there is no symptom improvement after 2 days of treatment.
  2) Toxic
    a) Laboratory Parameters
      1) Until further data are available regarding systemic toxicity, blood glucose and adrenal function assessment (cortisol levels, ACTH stimulation testing) should be considered during prolonged topical therapy by any route

## 4.2 Patient Instructions

A) LOTEPREDNOL (Into the eye)

Loteprednol

Treats redness, itching, or watering of the eyes caused by several conditions, including allergies, eye infection, herpes zoster, and eye surgery. Belongs to a class of drugs called corticosteroids.

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an allergic reaction to loteprednol or other corticosteroids. There are certain types of eye infection for which this medicine should not be used. Do not use loteprednol for any eye condition except the one your doctor prescribed it to treat.

How to Use This Medicine:

Drop

Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to. This medicine is not for long-term use. Using this medicine for longer than recommended can cause serious side effects.

Do not use the medicine for eye irritation that has not been examined by a doctor.

Wash your hands before and after using the medicine.

Shake the eye drops well just before each use.

Lie down or tilt your head back. With your index finger, pull down the lower lid of your eye to form a pocket.

To use the eye drops: Hold the dropper close to your eye with the other hand. Drop the correct number of drops into the pocket made between your lower lid and eyeball. Gently close your eyes. Place your index finger over the inner corner of your eye for 1 minute. Do not rinse or wipe the dropper or allow it to touch anything, including your eye. Put the cap on the bottle right away.

Never share your medicine with anyone.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose.

Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Keep the bottle upright when you are not using it.

Store the medicine at room temperature, away from heat and direct light.

After you have used this medicine for the length of time recommended by your doctor, throw any unused eye drops away.

Keep all medicine out of the reach of children.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Warnings While Using This Medicine:
If you are pregnant or breastfeeding, talk to your doctor before using this medicine.
Make sure your doctor knows if you have glaucoma or a history of herpes simplex, including herpes infection of the eye (keratitis).
Make sure your doctor knows if you have any other eye infections. This medicine can make certain types of infections worse.
If you have surgery for cataracts, be sure your surgeon knows you are using this medicine.
If you do not notice an improvement in your eyes after two days, call your doctor.
If you use this medicine for more than 10 days, your doctor will need to examine your eyes to make sure there are no unwanted effects.
Do not wear contact lenses while using Lotemax™.
Ask your doctor if you can wear contact lens while using Alrex™. If your eyes are not red, you may be able to wear your contacts.
Wait at least 10 minutes after putting the drops in your eyes before you insert the lenses.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Change in vision or loss of vision
Eye pain
Increased redness, swelling, or irritation
Increased sensitivity to light

If you notice these less serious side effects, talk with your doctor:
Burning when putting the drops in your eyes
Discharge from the eye
Dry eyes
Feeling that something is in your eye
Headache
Runny nose
Sore throat

If you notice other side effects that you think are caused by this medicine, tell your doctor.

## 4.3 Place In Therapy

A) Loteprednol etabonate, a "soft drug," is claimed to offer an advantage over conventional topically-used corticosteroids by virtue of its

rapid and essentially complete metabolism to inactive compounds after exertion of its therapeutic effect, thus potentially lessening systemic (or local) toxicity. The drug is indicated as an ophthalmic preparation in the treatment of conjunctival inflammatory conditions; other potential applications are skin conditions (cream, ointment), nasal use, colonic instillation, and asthma (inhalation).

**B)** However, metabolic pathways for loteprednol etabonate have not been determined in humans, and data from animal studies are conflicting. Although mechanisms of metabolism may prove to be moot as animal data suggest near-complete or complete metabolism following intraocular, oral, or intravenous administration (thus achieving the goal of a "soft drug"), clarification of the extent and rapidity of metabolism, and confirmation of only inactive metabolites, is needed in humans.

**C)** Despite the probable rapid conversion of loteprednol etabonate to inactive compounds, systemic or local toxicity with topically-applied conventional corticosteroids is not problematic in the majority of patients, and significant advantages of loteprednol may be difficult to demonstrate. Direct efficacy and toxicity comparisons of loteprednol etabonate and these agents (eg, dexamethasone, prednisolone) are needed to assess the potential role of this agent in all indications.

**D)** Loteprednol etabonate is not recommended for hospital formulary consideration until further studies are completed.

## 4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

**1)** Loteprednol etabonate is a glucocorticoid (prednisolone derivative) for topical use primarily in ocular conditions, such as allergic conjunctivitis and giant papillary conjunctivitis (Bartlett et al, 1993; Anon, 1995). The compound was designed to be a "soft steroid," an active compound which exerts a therapeutic local (antiinflammatory) effect and is then rapidly (completely) degraded to inactive metabolites, preferably in one metabolic step; this type of compound could avoid the local and systemic toxicity observed with conventional or "hard" steroids (Bodor et al, 1992; Hochhaus et al, 1992; Druzgala et al, 1991).

**2)** Synthesis of loteprednol etabonate was based on the inactive metabolite approach, where a nontoxic metabolite of a known active drug is identified and activated via chemical modification, forming the drug for clinical use. The activated form of the drug would undergo rapid and predictable conversion back to the inactive metabolite in vivo (Bodor et al, 1992; Hochhaus et al, 1992). The lead compound in the design of loteprednol etabonate was the inactive prednisolone metabolite, delta-1-cortienic acid (PJ-91); loteprednol etabonate was formed by carboxylation of delta-1-cortienic acid at the 17-beta position followed by addition of a 17-beta-chloromethyl ester function (activation step) (Druzgala et al, 1991a; Bodor et al, 1992; Druzgala et al, 1991).

**3)** It was expected that rapid esterase hydrolysis of the metabolically-labile 17-beta-chloromethyl ester function would occur in the circulation following systemic absorption, forming the more hydrophilic and inactive 17-beta-carboxylic acid derivative (known as PJ-91) and subsequently PJ-90 (Hochhaus et al, 1992; Druzgala et al, 1991; Bodor et al, 1992). However, metabolic studies in animals have provided conflicting data, and hepatic metabolism may contribute more to inactivation of the drug than plasma hydrolysis (Sloan & Perrin, 1994; Druzgala et al, 1991). Studies in rabbits suggest significant esterase metabolism of loteprednol etabonate in corneal tissue following ocular administration (Druzgala et al, 1991). Human studies are needed to delineate metabolic pathways that will occur clinically and confirm rapid formation of completely inactive metabolites.

B) GLUCOCORTICOID EFFECTS

**1)** Preclinical studies have demonstrated potent glucocorticoid activity of loteprednol etabonate, but inactivity of metabolites PJ-90 and PJ-91 (Druzgala et al, 1991a; Bodor et al, 1991; Howes et al, 1994). In glucocorticoid receptor binding studies (rat lung), the binding

affinity of loteprednol etabonate was 4 times that of dexamethasone; both compounds were shown to have a Hill factor of approximately 1 (Druzgala et al, 1991a).
2) Topical application of loteprednol etabonate 0.1% ophthalmic solution has been at least as effective as 0.1% dexamethasone sodium phosphate ophthalmic solution in reducing corneal scarring following experimentally-induced corneal damage in rabbits (Bodor & Varga, 1990). In a model of lipopolysaccharide-induced uveitis, loteprednol etabonate 0.5% was less effective than fluorometholone 0.1% or dexamethasone (concentration unspecified) in reducing inflammation, whereas a 1% solution of loteprednol etabonate compared well with fluorometholone 0.1% and dexamethasone in Freund's adjuvant-induced chronic uveitis (Howes et al, 1994). In other animal studies, the antiinflammatory activity of loteprednol etabonate 1% has approached that of prednisolone 1% (Bartlett et al, 1993).
3) No significant cortisol suppression was observed in 10 healthy volunteers receiving ophthalmic loteprednol etabonate 0.5% suspension for up to 42 days (Howes & Novack, 1998). Similarly, no significant adrenal suppressive effects have been reported in animals following prolonged topical application or oral administration of loteprednol etabonate (Bodor & Varga, 1990; Bodor et al, 1992). Loteprednol etabonate may have a lower propensity to raise intraocular pressure than other topical corticosteroids (Bartlett et al, 1993a), although this requires confirmation.

## 4.5 Therapeutic Uses

### 4.5.A Loteprednol Etabonate

Giant papillary conjunctivitis
Inflammatory disorder of the eye
Seasonal allergic conjunctivitis

#### 4.5.A.1 Giant papillary conjunctivitis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in giant papillary conjunctivitis associated with contact lenses
Contact lenses may be worn during treatment

c) Adult:

1) LOTEPREDNOL ETABONATE 0.5% ophthalmic suspension, 1 drop instilled 4 times daily for 6 weeks, was effective and well-tolerated in a double-blind, placebo-controlled study of 223 patients with contact-lens associated giant papillary conjunctivitis. Patients refrained from wearing their contact lenses for the first 2 or 3 days of therapy, and resumed daily wear thereafter. Papillary response rates were 78% among patients in the loteprednol group and 51% among placebo patients (p less

than 0.001). Itch relief also was significantly better with loteprednol versus placebo (95% vs 81%; p=0.001); at end of study, 70% of active treatment patients had an itch score of zero. There was a trend (p=0.053) toward loteprednol superiority over placebo in relieving lens intolerance. Loteprednol was associated with a mild and transient increase in intraocular pressure, that resolved upon completion of therapy and was not considered serious (Friedlaender & Howes, 1997).

2) LOTEPREDNOL ETABONATE 0.5% ophthalmic suspension (1 drop 4 times daily) was effective in the treatment of contact lens-associated giant papillary conjunctivitis in a 28-day, double-blind, placebo-controlled study (n=110). The drug was significantly superior to placebo in reducing the severity of papillae scores from the 7th to the 28th day of treatment; on day 28, 16% of the loteprednol group versus 2% of the placebo group were free of papillae. However, baseline severity scores were greater in the loteprednol group, which may have influenced outcome. Overall, there was no between-group difference in relief of itching and improvement in bulbar and palpebral conjunctival injection. However, in a subset of patients who were allowed to continue wearing contact lenses during treatment, loteprednol etabonate was more effective than placebo in improving papillae scores and bulbar and palpebral conjunctival injection, but not itching. Although investigators judged loteprednol etabonate to be significantly superior to placebo for overall improvement, subjective patient assessments did not reveal a significant difference (Bartlett et al, 1993b).

**4.5.A.2 Inflammatory disorder of the eye**

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated in steroid-responsive and postoperative conjunctivitis (0.5% ophthalmic suspension)
Indicated in seasonal allergic conjunctivitis (0.2% ophthalmic suspension)

c) Adult:

1) Loteprednol etabonate 0.5% ophthalmic suspension (Lotemax(TM)) is a site-specific corticosteroid indicated to treat steroid-responsive CONJUNCTIVITIS resulting from conditions such as superficial punctate keratitis, herpes zoster keratitis, as well as postoperative conjunctivitis after ocular surgery (Prod Info Lotemax(TM), 1998b). Loteprednol etabonate 0.2% ophthalmic suspension (Alrex(TM)) is indicated to treat SEASONAL ALLERGIC CONJUNCTIVITIS (Prod Info Alrex(TM), 1998).

2) In a placebo-controlled trial, 0.5% loteprednol etabonate was statistically superior in treating anterior chamber inflammation in patients who had undergone cataract surgery and intraocular lens implantation. Of the 222 assessable patients, 109 were randomized to loteprednol and 113 received placebo. The dosage of one drop per eye was begun the day after surgery and continued on a schedule of 4 times daily (every 4 hours) during waking hours for 14 days. Systemic and ocular medications

were allowed to be continued during the study period, including oral non-steroidal anti-inflammatory medications and ocular anti-infectives. In the loteprednol group, 64% of patients had resolution of cell and flare after treatment, compared with 29% of placebo patients (p less than 0.001). The rates of resolution at each of the four examinations during treatment also favored loteprednol over placebo (p=0.003). Several days after treatment ended, 84% of patients receiving loteprednol remained unchanged or showed improvement in anterior chamber inflammation from visit 4. Regardless of treatment group, resolution of anterior chamber inflammation was more likely in patients with light irides than in those with dark irides. Loteprednol was well-tolerated, with only one patient discontinuing treatment because of adverse effects. Intraocular pressure decreased a mean of 2 millimeters Hg in all patients, with no between-group difference. Six percent of the loteprednol-treated patients versus 30% of placebo-treated patients were considered to have failed treatment (p less than 0.001) (Stewart et al, 1998).

#### 4.5.A.3 Seasonal allergic conjunctivitis

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Loteprednol 0.2% ophthalmic suspension is indicated to treat SEASONAL ALLERGIC CONJUNCTIVITIS (Prod Info Alrex (TM), 1998)

c) Adult:

1) In a 6-week, double-blind study of adult patients with seasonal allergic conjunctivitis, loteprednol etabonate 0.2% ophthalmic suspension was significantly more effective than placebo in suppressing primary and secondary symptoms. Sixty-six patients were randomized to active drug and 67 received placebo every 4 hours while awake. At 2 weeks, 79% of loteprednol patients and 47% of placebo patients were considered fully or mostly controlled (p less than 0.001). The therapeutic advantage of loteprednol was significant not only for primary symptoms of bulbar conjunctival injection and ocular itching, but also for secondary symptoms such as photophobia, burning and stinging, foreign body sensation, erythema, and palpebral conjunctival injection. None of the patients in this study had an elevation of greater than 10 mmHg in intraocular pressure; one patient in the loteprednol group had a 9 mmHg elevation and withdrew from the study. Another patient in the loteprednol group withdrew after having an acute pharyngeal reaction with headache (Dell et al, 1998).

## 4.6 Comparative Efficacy / Evaluation With Other Therapies

#### 4.6.A Prednisolone

Acute anterior uveitis

Uveitis

**4.6.A.1 Acute anterior uveitis**

a) Loteprednol etabonate 0.5% ophthalmic suspension was less effective than prednisolone acetate 1% ophthalmic suspension in the treatment of acute anterior uveitis. In the first controlled study, data on United Kingdom participants were omitted and only the U.S. results (n=70) were reported. The dosing regimen for both drugs consisted of 8 times/day dosing for the first week, 6 times/day for the second week, 4 times/day for the third week, then a final 2-week taper if the condition had resolved. Signs and symptoms decreased in both groups, with significantly more prednisolone-treated patients achieving complete relief of photophobia (84% versus 62%, p=0.035). A second controlled trial (n=175) used a more intensive dosing regimen during the first 2 weeks: hourly (up to 16 times/day) for the first week, then every 2 hours (up to 8 times/day) for the second week, and continued gradual tapering through week 4. The proportions of patients with anterior chamber cell resolution (87% versus 72%, p=0.015) and flare resolution (82% versus 66%, p=0.017) were significantly higher in the prednisolone group. Intraocular pressure increases of at least 10 millimeters of mercury were less common with loteprednol across both studies (1 versus 7 patients) (Anon, 1999).

**4.6.A.2 Uveitis**

a) Results of 2 controlled studies demonstrated that prednisolone 1% ophthalmic suspension (OS) was more effective than loteprednol 0.5% OS for treating acute anterior uveitis; however, fewer patients receiving loteprednol than prednisolone developed an elevated intraocular pressure (Anon, 1999). Patients in study 1 (n=66) were randomly assigned to receive prednisolone 1% OS or loteprednol 0.5% OS 8 times daily on days 0 to 7, 6 times daily on days 8 to 14, 4 times daily on days 15 to 21, and after day 21 tapering depending on disease severity. In study 2 (n=170), the dosage regimen was as follows: (1) days 0 to 7 - every hour, (2) days 8 to 14 - every 2 hours, (3) days 15 to 21 - 4 times daily, (4) days 22 to 25 - twice daily, and (5) days 26 to 28 - once daily. By the final visit in study 1, 74% and 88% of patients treated with loteprednol and prednisolone, respectively, had resolution of anterior chamber cells (p=0.194); whereas, in study 2, 72% and 87% of patients treated with loteprednol and prednisolone, respectively, had resolution of anterior chamber cells (p=0.015). In study 2, an increase in intraocular pressure greater than 10 millimeters of mercury was reported in 6 patients treated with prednisolone versus 1 patient treated with loteprednol. Although less effective than prednisolone, loteprednol may be a useful and safer treatment than prednisolone for many patients with acute anterior uveitis.

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